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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/376,774	08/17/99	FUNG Y	D6087

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EXAMINER	
ZARA, J	
ART UNIT	**PAPER NUMBER**
1635	6

DATE MAILED: 10/24/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

File

Office Action Summary

Application No.	Applicant(s)
09/356,774	Fung et al.
Examiner	**Group Art Unit**
Zara, Jane	1635

☒ Responsive to communication(s) filed on *Sep 28, 2000*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-28* is/are pending in the applicat

Of the above, claim(s) *4-28* is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-3* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☒ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

☒ Notice to Comply

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

This office action is in response to the communication filed on September 27, 2000, as Paper No. 5. Claims 1-28 are pending in the instant application.

Claims 4-28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected Groups, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 5.

Specification

The specification is objected to on page 12, line 1, because the terms "tetp-" and "ptet-" appear to be used interchangeably. Appropriate correction or clarification is required.

The specification is objected to on page 12, lines 5-10 and 13, because, in the description of Figure 1, the term "TET-ON" is used in the text, while the terms "TET-ON" and "TAKON" are used apparently interchangeably in the figure. Appropriate clarification or correction is required.

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. No

sequences which are described in the claims or throughout the specification have sequences which are fully disclosed along with the appropriate SEQ ID Nos identifying them. See the accompanying Notice to Comply. Applicant is requested to return a copy of the attached Notice to Comply with the reply.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are those which describe where the heterologous gene is to be inserted into the vector (i.e. in relation to the regulatory elements listed in claim 1). Furthermore, the "vector" mentioned in claims 2 and 3 needs to be further delineated or described.

Claims 2 and 3 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are those which are involved in achieving sustained expression of a gene within the vector of claims 2 and 3.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to

> make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2 and 3 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of achieving sustained expression of a gene comprising the administration of the recombinant vector pDATH-X in cells *in vitro*, does not reasonably provide enablement for such sustained expression *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to a method of achieving sustained expression, in an organism, of a gene which is under the control of a heat or light inducible promoter, comprising the administration of the recombinant vector pDATH-X comprising the gene to be delivered and further comprising the administration of heat or light energy to said organism.

The following factors have been considered in determining that the specification does not enable the skilled artisan to make and/or use the invention over the scope claimed. This determination is based on several factors which, when considered together, illustrate that the art of gene delivery is highly unpredictable. The discussion is also based on references whose teachings show that, despite a tremendous amount of experimentation by highly skilled artisans in the field of gene delivery and expression *in vivo*, there remain significant hurdles known in the art to make and/or use the invention over the scope claimed.

The nature of the invention. Methods of targeting nucleic acids into host cells *in vivo* fall into the broad area known as gene therapy methods. While delivery of nucleic acids in and

of itself is not considered therapy *per se*, delivery shares many of the obstacles recognized for the actual therapy methods because successful therapy methods are for the most part based on the ability to deliver exogenous genes in functional form to cells or tissues of interest.

The state of the prior art and the predictability or unpredictability of the art. The following references are cited herein to illustrate that the art of gene delivery is highly unpredictable. Crystal, in discussing the art of gene therapy, describes the "ideal gene transfer vector" to have among its attributes the ability to efficiently transfer genes and be specific for its target. Crystal furthermore teaches that the disadvantages of gene therapy or delivery include general inefficiency at achieving successful gene transfer as well as a general lack of available data regarding repetitive administration of DNA to whole organisms (page 405, second paragraph). Another major obstacle for *in vivo* delivery is to ensure delivery of the bioactive agent in sufficiently high numbers to appropriate target cells to be effective when administered *in vivo*. The delivery of genes to adequate numbers of target cells, for instance, and/or ensuring sufficient and appropriate gene expression in those cells are major difficulties for gene therapy methods (i.e. see Crystal on page 409, center column). The same is true for the instant invention comprising inducible gene transfer vehicles for gene delivery. The specification as filed teaches that the ability to tightly control tetracycline induced expression *in vivo* is difficult due to tissue heterogeneity and that generally the pharmacokinetics of tetracycline varies within individual organisms as well as within tissues of a given individual (pages 36 and 41 of the specification).

A further difficulty in gene delivery is the unpredictable nature of gene therapy when one tries to extrapolate from animal models to human systems. Long lists of clinical trials exist which have yet to yield therapeutic benefits. Crystal points out that "no human disease has been cured by human gene transfer and it is not clear when this will be accomplished" (page 407, first column). Schofield *et al* teach advantages of various methods of *in vivo* delivery of genes, while also stressing that many of the details regarding cell targeting, cell entry and gene expression in target cells remain highly speculative. Furthermore, Schofield *et al* caution that *significant variations exist between animals*, and state that only limited conclusions could be drawn from animal studies which may be applied to the treatment of humans (pages 61-64). Verma *et al* teach the problems of gene delivery in whole organisms using non-viral vector approaches, using various delivery agents, and state that such approaches suffer from limitations relating to poor efficiency of delivery and the transient expression of delivered genes (page 239, second paragraph from the end). Friedmann teaches that non-viral gene transfer is much less efficient than virus-mediated transfer (page 100, last paragraph-page 101, first paragraph), while, according to Friedmann, the gene therapy field as a whole currently lacks convincing therapeutic benefit (page 96). Branch and Crooke teach that the *in vivo* (whole organism) application of nucleic acids (such as antisense) is a highly unpredictable endeavor due to target accessibility and delivery issues. Crooke also points out that cell culture examples are generally not predictive of *in vivo* inhibition of target genes. (See entire text for Branch and especially pages 34-36 for Crooke).

While these references acknowledge the usefulness of gene therapy and gene delivery using recombinant viral and non-viral vectors and the possibility of developing efficacious strategies in the future, they also illustrate that there are numerous obstacles to successful therapy which current methods still must overcome, including the added limitations of utilizing inducible vectors whereby the appropriate delivery of antibiotics, heat or light is also highly unpredictable. As such, the disclosed utilities of the present specification which are drawn to a method of achieving sustained gene expression comprising the administration of a vector containing a heat or light inducible promoter in combination with tetracycline derived repressor and promoter elements are credible. The present rejection, therefore, is not for lack of utility, but rather for lack of enablement for the scope of the methods claimed.

The amount of direction or guidance presented in the specification and the presence or absence of working examples. Applicants have not provided guidance in the specification toward a method of delivering any and/or all genes via administration of the inducible vector pDATH-X to appropriate target cells in any organism and further comprising the administration of heat or light such that the gene is delivered to the appropriate target cells and sustained gene expression is obtained.

The specification teaches the *in vitro* expression of p53 in target cells *in vitro* following the administration of the pDATH vector comprising the heat shock promoter-tetp and further comprising the administration of doxorubicin and light, whereby p53 expression is sustained (i.e. as illustrated in Figure 8). The specification fails to teach the *in vivo* administration of

pDATH-X, doxorubicin (or other tetracycline analogue), and heat or light such that the target gene is appropriately delivered and expressed in target cells and further whereby target gene expression is sustained in view of the lack of guidance in the specification and the known unpredictability associated with the delivery and sustained expression of any and/or all genes in any and/or all target cells in a whole organism comprising the administration of a vector containing a heat or light inducible promoter in combination with antibiotic inducible and repressible promoters and further in combination with dominant negative genes and antisense, and further comprising the administration of appropriate amounts of antibiotics and heat or light to that organism.

The breadth of the claims and the quantity of experimentation required. The breadth of the claims is very broad. The claims are drawn to a method of achieving sustained expression of any and/or all genes comprising the administration of the recombinant vector pDATH-X to an organism in conjunction with the administration to said organism of heat or light energy. In order to practice the invention over the scope claimed, it would require trial and error or undue experimentation beyond which is taught in the specification to practice the invention drawn to the sustained expression of any and/or all genes in the appropriate target cells of any and/or all organisms comprising the administration of the recombinant vector pDATH-X in combination with the appropriate amounts of either heat or light and further in combination with the appropriate amount of antibiotic such that the gene is delivered to appropriate target cells, the gene is appropriately expressed, or in the case of antisense, the target gene is

appropriately inhibited, and further that sustained expression of the delivered gene is obtained. The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of accessible target sites for the appropriate target cells, modes of delivery and formulations to target appropriate cells and/or tissues whereby the gene is delivered and further whereby sustained expression of the gene is obtained upon proper administration of the pDATH-X vector, heat or light and antibiotic to the organism. Since the specification fails to provide any particular guidance for the successful delivery of any and/or all genes which have been subcloned into pDATH-X vector whereby they are administered appropriately with heat or light and further with the appropriate amount of antibiotic to any and/or all target cells in any and/or all organisms, and since determination of these factors for a particular gene, source of heat or light energy and antibiotic is highly unpredictable for a particular organism, it would require undue experimentation to practice the invention over the scope claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reeves *et al* and Cigan *et al*, the combination in view of Voellmy *et al* and further in view of Szaframski *et al* insofar as the claims are drawn to a method of achieving sustained expression of a (heterologous) gene *in vitro*, which gene is under control of a heat or light inducible promoter comprising the administration of the recombinant vector pDATH-X, which vector comprises the heterologous gene to be delivered as well as comprising various regulatory circuits comprising at least one tetracycline controlled transactivator responsive promoter, tetracycline resistance operon regulatory elements, DNA encoding an antisense orientation relative to DNA encoding the tetracycline regulator unit, and which gene to be delivered is under the control of the tet operator and the pCMV promoter, which vector further comprises a fusion of the tetracycline repressor and the transcription activation domain of the VP16 protein, which tetracycline repressor is under control of the heat shock promoter, the tet operator binding site and the pCMV promoter, a dominant negative tet repressor lacking the VP16 transactivation domain under the control of the pCMV promoter, and which sustained gene expression further comprises the administration of heat or light energy.

Reeves *et al* teach a tetracycline regulated inducible retroviral vector for the controlled delivery of a gene product, which vector comprises the tetracycline controlled transactivator responsive promoter, tetracycline resistance operon regulatory elements embedded within a minimal pCMV promoter, a second regulatory component comprising a fusion of the tetracycline repressor and the transactivator protein VP16, as well as a third regulatory component comprising DNA encoding the tetracycline response unit in an antisense orientation, whereby the heterologous gene is under the transcriptional control of a third promoter and further whereby the addition of tetracycline either increases of inhibits the expression of the heterologous gene (column 1, line 38-column 3, line 61; figure 1).

Cigan *et al* teach genetic constructs comprising a tissue specific promoter, which promoter controls the expression of a DNA sequence encoding a gene product, a dominant negative gene and a nucleotide sequence encoding a transcriptional activator linked to a DNA binding protein, whereby the DNA binding protein binds to the operator and activates transcription of said dominant negative gene (column 1, lines 12-23; column 4, lines 11-67; column 7, lines 11-59).

The primary references do not teach the incorporation of heat shock promoter elements into regulatory circuits, nor of the use of heat shock promoter elements in combination with tetracycline derived control elements in regulatory circuits for controlled, inducible, heterologous gene expression.

Voellmy *et al* teach the efficient heat controlled expression of a heterologous gene in mammalian cells, which gene was under the control of the heat shock promoter (abstract, second and third paragraphs on the right on page 4949; section entitled *Heat regulated expression of the cloned human gene* on pages 4950-4951).

Szafranski *et al* teach methods of compensating for the incomplete repression of regulatory promoters (i.e. leaky promoters) comprising the inclusion of additional regulatory components into gene delivery vehicles, which additional control components include expression of antisense which target the inadvertent overexpression of sense gene sequences due to leaky promoters (column 5, line 48- column 6, line 41).

It would have been obvious to one of ordinary skill in the art to utilize heat or light inducible vectors for the introduction and sustained expression of a desired gene sequence in a target cell *in vitro* comprising the administration of the inducible vector in combination with the administration of heat or light because the efficient heat controlled expression of a heterologous gene in mammalian cells, which gene was under the control of the heat shock promoter, was taught previously by Voellmy *et al*. One of ordinary skill in the art would have been motivated to incorporate other regulatory circuits into such a heat or light inducible gene transfer vehicle because inducible promoter leakiness is well known in the art (i.e. as had been taught by Szafranski *et al* and others), and the incorporation of multiple regulatory circuits into inducible gene transfer systems had been taught by Reeves *et al*, which circuits include tetracycline controlled transactivator responsive promoter elements, tetracycline resistance operon regulatory

elements embedded within a minimal pCMV promoter, fusions of the tetracycline repressor and the transactivator protein VP16, as well as other regulatory components such as DNA encoding the tetracycline response unit in an antisense orientation, whereby the addition of tetracycline either increases of inhibits the expression of a heterologous gene. One of ordinary skill in the art would have expected that the further incorporation of a regulatory dominant negative gene within this regulatory circuit would further abrogate promoter leakiness, because the expression of such a regulatory protein as a result of undesired (i.e. uninduced or overinduced upstream) gene expression provides an added negative feedback mechanism as had been taught by Cigan *et al.* One of ordinary skill in the art would have expected therefore that the combined regulation afforded by the heat or light inducible, antibiotic inducible recombinant vector pDATH-X leads to the sustained expression in target cells of a heterologous gene subcloned appropriately into said vector, whereby light or heat is administered to the target cells in combination with pDATH-X.

Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R.

§ 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(703) 306-5820.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. George Elliott, can be reached on (703) 308-4003. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

JZ

October 16, 2000

ROBERT A. SCHWARTZMAN
PRIMARY EXAMINER

File Application No.: 09/376,774

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.

☒ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☒ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☐ 7. Other: _____

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ **An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.**

☒ **A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).**

For questions regarding compliance to these requirements, please contact:

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